Abstract

Background: Germline mutations in the tumor suppressor gene, BAP1, a deubiquitinase that regulates key cellular pathways, are associated with a broad spectrum of diseases. The described tumor predisposition syndrome characterized by early onset benign melanocytic skin tumors, and a significant risk of cancers that include melanoma, cutaneous and uveal melanoma, renal cell carcinoma (RCC) and cholangiocarcinoma. Somatic or germline BAP1 mutations have been associated with an aggressive course and a poor prognosis in RCC and cholangiocarcinoma and may render the cancers more sensitive to HDAC inhibitors or Parp inhibitors. We investigated types and frequencies of BAP1 mutations in a large cohort of diverse malignancies and their associations with other molecular/genomic characteristics.

Results: A total of 9782 tumor samples from over 40 cancer types were molecularly profiled at Caris Life Sciences by next generation sequencing (Illumina NextSeq platform and Agilent SureSelect XT panel, 592 genes). Microsatellite instability (MSI) was tested by PCR and fragment analysis (Promega MS1 Analysis System).

Methods: A pathogenic somatic or germline BAP1 mutation was identified in 20 cancer types, with a total of 129 tumors with mutations found (1.3% prevalence). As expected, BAP1 mutations were frequently seen in uveal melanoma (52% or 24 in 48), malignant pleural mesothelioma (29% or 6 in 21), RCC (8% or 12 in 150), cholangiocarcinoma (6.6% or 13 in 196), and cutaneous melanoma (2.2% or 7 in 319). In addition, pathogenic BAP1 mutations were detected in carcinomas arising in parotid gland (10.3% or 3 in 29), anus (8.3% or 3 in 36), cervix (3.4% or 319). In addition, pathogenic BAP1 mutations were detected in carcinomas arising in parotid gland (10.3% or 3 in 29), anus (8.3% or 3 in 36), cervix (3.4% or 319), stomach (3.3%, or 6 in 180), head and neck (2 in 97 or 2%), lung (14 in 1590 or 0.9%), and breast (0.8% or 7 in 887). A mutation was also noted in a meningioma (1 in 45) and a uterine sarcoma (1 in 98). Variants of BAP1 (pathogenic, presumed pathogenic, and variants of unknown significance) were more often seen in MSI-high tumors (compared to MSI-) in both colorectal (12/65 vs. 18/1003) and endometrial carcinomas (5 of 69 vs. 5 of 521, both p<0.05). It was not determined whether the BAP1 mutations were somatic or germline in origin.

Conclusions: The study confirmed the presence of pathogenic BAP1 mutations in carcinomas commonly associated with BAP1 germline and somatic mutations. It also identified BAP1 mutations in additional cancer types (pancreatid gland, anal and cervical carcinomas), as well as its association with MSI-H cancers (colons and endometrium). Evaluation of mutations in non-cancerous tissues is underway to determine if these novel cancer associations are related to germline predisposition.

Introduction

BAP1 (BRCA1 associated protein 1) is a deubiquitinase required for efficient assembly of the homologous recombination proteins (BRCA1 and RAD51) at ionizing radiation-induced foci, and promotes error-free repair of these lesions (1). BAP1 tumor predisposition syndrome (BAP1-TPDS) is caused by a heterozygous germline pathogenic variant in BAP1 gene. It is associated with an increased risk for atypical Spitz nevi and (in descending order of frequency): uveal (eye) melanoma (UM), malignant melanomas (MM), cutaneous melanomas (CM), clear cell renal cell carcinoma (CCRC), and basal cell carcinoma (BCC). Other suspected but yet unconfirmed tumors in BAP1-TPDS include: breast cancer, cholangiocarcinoma, non-small-cell lung adenocarcinomas (NSCLC), meningioma, and neuroradionecrosis (2-4).

Table 1: Number of BAP1 mutations seen. A total of 197 pathogenic mutations were seen in the 14,837 tumors interrogated. Most frequent alterations seen are frame-shift and nonsense mutations, followed by intronic mutations that disrupt conserved splice sites.

Results (Continued)

Figure 1. A total of 14,837 tumors of 49 cancer types were tested with NextGen (NextSEQ) and the top 27 cancer types of the highest BAP1 mutation frequency are shown in the parentheses. Percentages next to the bars represent the frequency of pathogenic mutations.

Table 2: A – retained expression of BAP1 in endometrial adenocarcinoma (G470R, 90% a.) in a germ line carrier (G470R 50% allele frequency in normal tissues). B – Loss of expression of BAP1 in RCC (BAP1D648S) is an example of pathogenic mutation with the loss of protein expression.

References


Conclusion

1. Interrogation of a large cohort (N=14,837) of solid tumors from a variety of cancers (49 organs/cancer types) reveals BAP1 mutations in 26 different cancer types.
2. In addition, to known BAP1-associated cancers (including uveal and cutaneous melanoma, malignant pleural mesothelioma, kidney cancer and cholangiocarcinoma), pathogenic BAP1 mutations were also seen in 6% of all cancer, 4% of cancer with unknown primary and 3% of pancreatic cancer, rectal cancer, renal cell and liver cancer.
3. Most frequently observed mutations of BAP1 are frame-shifts, nonsense mutations and intronic mutations that alter splice sites; missense mutations are rare.
4. Loss of protein expression is seen to associate with frameshift mutations while retained protein expression is seen in germline BAP1 point mutation cases.
5. Evaluation of mutations in non-cancerous tissues is underway to determine if these novel cancer associations are related to germline predisposition.